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09/163,289	09/29/1998	HARRY C. DIETZ	07265/098002	9819

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EXAMINER	
SCHMIDT, MARY M	
ART UNIT	PAPER NUMBER
1635	24

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/163,289	Applicant(s) DIETZ, HARRY C.	
	Examiner Mary Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 1998* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on May 15, 2002, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/163,289 is acceptable and a CPA has been established. An action on the CPA follows.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-13 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is broadly drawn to any nucleic acid construct for suppressing gene expression comprising in 5' to 3' orientation: an unmodified 5' stem loop structure; an antisense nucleic acid; and an unmodified 3' stem loop structure, wherein the antisense nucleic acid is flanked by the stem loop structures. Claims 2-12 add the following limitations: wherein the unmodified stem loop structures are unmodified U snRNA structures; wherein the U snRNA is U1; further

comprising a promoter; such as a U1 snRNA promoter, a constitutive promoter, an inducible promoter; further comprising a ribozyme nucleic acid, such as located between the 5' and 3' stem loop structures, such as a hammerhead-type ribozyme, having a consensus sequence of 5'-GUC-3" or 5'-GUA-3'; wherein the antisense nucleic acid is selected from the group consisting of rent-1, HPV E6, HIV, hyaluronic acid synthase, and fibrillin. Claims 13 and 15 are drawn to methods of suppression of gene expression in a cell comprising administering to the cell in vitro a suppressive-effective amount of the nucleic acid construct of claim 1, whereby expression of the gene is suppressed in the cell; further comprising administering a modified nucleic acid encoding a wild-type polypeptide corresponding to the gene product of the gene being suppressed, wherein the modified nucleic acid is resistant to ribozyme cleavage and/or antisense inhibition.

The specification teaches by way of example antisense constructs flanked by 5' and 3' U1 snRNA stem loop structures (pages 23-29 of the specification). The specification does not teach that Applicant was in possession of a representative number of species of the claimed constructs at the time the invention was made for the following reasons:

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> **The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed**

correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The claims as written, given their broadest possible interpretation, read on a nucleic acid sequence of any undefined length having at least (in view of the open "comprising" language) two stem loop structures, one on each side of an antisense sequence. The stem loop structures may be of any size and sequence composition, and the antisense or ribozyme-antisense sequence(s) may be of any length and sequence composition. The method claims, 13 and 15, are methods for suppression of any gene via administering *in vitro* a suppressive-effective amount of the nucleic acid of claim 1.

In regard to the claimed stem loops, the specification as filed does not teach identifying characteristics of the structures of any other stem loops other than the U1 snRNA stem loops. One of skill in the art would not know what other possible stem loops would be functional equivalents to the U1 snRNA stem loops from the teachings of the specification as filed. One of skill in the art would not have been able to readily envisage other types of stem loops that would

function similarly to the U1 snRNA stem loops for use in conjunction with the antisense and/or ribozyme sequence(s).

In regard to the different antisense and/or ribozymes sequences which bind and target different gene sequences, the specification as filed did not describe how any newly designed or previously known antisense and/or ribozyme-antisense (ie. antisense or ribozymes taught in the prior art) could function having any such flanking stem loops as claimed in instant claim 1. The written description requirement for this claimed genus of any antisense or ribozyme-antisense having the flanking sequences has not been satisfied by the teachings of the instant specification because a sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, coupled with a known or disclosed correlation between the gene suppression function and the unmodified stem loop flanking structure was not taught in either the specification or the prior art at the time the invention was made.

In the absence of a more specific description of the design criteria (ie., specific sequences or more specific types of stem loop structures having specific sequences) as well as the combined need for the antisense or ribozyme-antisense structures to function as claimed, for suppressing gene expression, one skilled in the art would not have recognized that Applicant was in possession of a representative number of species of the entire breath of nucleic acid compositions claimed. It was art recognized at the time the invention was made that specific features of

antisense and ribozymes are necessary for antisense and ribozyme function in cells in culture for instance. Without knowing features such as a specific size length of the antisense or ribozyme which binds to the target sequence, the specific sequence and placement of ribozymes for cleavage of the target sequence, stem loops that would not create steric hindrance so that the antisense and/or ribozyme would still be able to reach the target and bind, for instance, one would not be able to make the claimed compounds.

Since neither the specification as filed nor the prior art teach a representative number of species of any such nucleic acid construct as claimed, one of skill in the art would not have recognized that Applicant was in possession of the breath of claimed compounds at the time the invention was made.

Please note, Applicant was considered in possession of the breath of claimed compounds allowed in the parent Application, U.S. Patent No. 5,814,500.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 1-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Michienzi et al. for the same reasons of record as set forth in the Official Actions mailed 7/17/01 and 8/29/00.

Michienzi et al. teach a U1 snRNA ribozyme vector structure for suppressing Rev gene (an HIV gene) in cells in culture. They teach the specific use of the U1 snRNA as "an effective vector for the efficient expression and delivery of ribozymes in the nuclear compartment." (Page 7223) The compositions of Michienzi et al. in figure 1 (page 7221) comprise an unmodified 5' stem loop structure (from U1 snRNA) flanking an antisense/ribozyme (hammerhead-type, with a consensus of 5'-GUC-3' in the target Rev pre-mRNA) and an unmodified 3' stem loop flanking antisense/ribozyme (a ribozyme is art recognized as having "antisense" function, only it inhibits the target via actual cleavage). They teach the original sequence of the U1-RNA in figure 1 in a side-by-side comparison of the U1 snRNA before and after the placement of the hammerhead ribozyme/antisense into section III of the ribozyme. The instant specification as filed defines on page 7 "unmodified" as "the folding pattern of the stem loop structure is not compromised by alterations in the nucleic acid sequence of the naturally occurring molecule. For example, it is understood that alterations which include, but are not limited to, mutations, insertions, deletions and substitutions of one or more nucleotides can be made within the sequence of the stem loop, as long as the stabilization function and hairpin formation of the stem loop is maintained." In view of this definition, the teachings of Michienzi et al. clearly read on the claimed "unmodified" constructs since the U1 snRNA stem loops of Michienzi et al. that flank the ribozyme are not modified. The constructs were subcloned into vectors having various promoters T7, U1 snRNA gene promoter, and *X. laevis* L14 ribosomal protein gene promoter (pages 7219-7221) for use in

X. laevis. They teach temperature dependant activity of the vector constructs and administration of the constructs to cells in cell culture.

Michienzi et al. thus anticipate the claimed invention of claims 1-13.

6. Claim 15 is considered free of the prior art since Michienzi et al. taught *X.laevis* cells injected with vectors expressing the HIV Rev gene (page 7220) and administering a modified and unmodified ribozyme U1 snRNA construct, but did not teach administration of a modified nucleic acid encoding a WT polypeptide corresponding to the gene product being suppressed wherein the modified nucleic acid is resistant to ribozyme cleavage and/or antisense inhibition as claimed.

Response to Arguments

Applicant's arguments filed 5/15/02 have been fully considered but they are not persuasive.

Applicant states that "Applicant's invention distinguishes over the prior art by reciting a nucleic acid construct for suppressing gene expression comprising an unmodified 5' stem loop structure, an antisense nucleic acid, and an unmodified 3' stem loop structure, wherein the stem loop structures flank the antisense nucleic acid. In contrast, Michienzi teaches nucleic acid constructs in which the stem loop III of U1 snRNA is modified by the addition of a hammerhead ribozyme within the actual stem loop structure. Accordingly, all constructs taught by Michienzi

contain modified stem loop structures, wherein Applicant's constructs contain unmodified stem loop structures."

In response, as quoted above, the instant specification as filed defines the "unmodified" stem loop structures as any stem loop wherein "the folding pattern of the stem loop structure is not compromised by alterations in the nucleic acid sequence of the naturally occurring molecule. For example, it is understood that alterations which include, but are not limited to, mutations, insertions, deletions and substitutions of one or more nucleotides can be made within the sequence of the stem loop, as long as the stabilization function and hairpin formation of the stem loop is maintained." Therefore, the insertion of the ribozyme taught by Michienzi in the U1 snRNA sequence, is embraced by the definitions of "unmodified" in the instant specification (page 7) which actually allows for modifications in the unmodified stem loops so long as function is retained. Michienzi et al. did teach that function was maintained of the U1 snRNA stem loops. Further, the stem loops of the flanking U1 snRNA stems on either side of loop III, are unmodified. Therefore, all the claimed limitations are met for unmodified stem loops flanking the antisense/ribozyme in the teachings of Michienzi et al.

Thus, while it is understood that the U1-Rz construct referred to in Figure 1 of Michienzi et al. does have the ribozyme placed in stem-loop III of the U1 snRNA, this does not render the U1-Rz construct "modified" in view of Applicant's definition in the specification recited above. The figure clearly shows one flanking hairpin on either side of the ribozyme site that is unmodified.

It is further understood that Michienzi's "modified" construct is the modification of the ribozyme, not the U1 snRNA, to make a construct having an inactive ribozyme as a control (the U1-Rz_m) construct in contrast to the "unmodified" U1-Rz constructs having functional ribozymes. However, as argued above, these "unmodified" constructs taught by Michienzi et al. are embraced by Applicant's definition of "unmodified" on page 7 of the instant specification.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Kay Pinkney*, whose telephone number is (703) 305-3553.

M. M. Schmidt
July 28, 2002

MM Schmidt